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Impact on Psychomotor Functions by Sedative Agents Used During Daycare Surgeries: A Randomized Controlled Double-Blinded Study of Dexmedetomidine Versus Midazolam-Fentanyl

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Sedative agents are used during surgeries to reduce stress and anxiety and discomfort of the patient. An ideal sedation agent should provide a rapid onset of action and faster recovery. Almost all commonly used sedative agents in daycare surgeries affect the cognitive and psychomotor functions. The research question of this study was to find out which of the commonly used sedative agents- Dexmedetomidine or Midazolam-Fentanyl combination produces less impact on the psychomotor functions of the patients. Seventy two patients who were undergoing tympanoplasty under local anesthesia, were randomly divided into two equal groups - Group D (dexmedetomidine) and Group MF (midazolam and fentanyl) using a computer-based randomization scheme. Group D received dexmedetomidine till an adequate sedation score was achieved (Ramsay sedation scale =3). Group MF patients received midazolam and fentanyl till an adequate sedation score was achieved. Baseline psychomotor assessment and delirium assessment was done 30 minutes prior to the shifting of the patient to operation theatre. All the scores were compared at 30 minutes, 1 hour, 2 hours, 4 hours and 8 hours by using MMSE test and stroop color word interference test for psychomotor assessment and short-CAM & Short-CAM severity test for delirium assessment. Statistical analysis was done by applying paired t-test and repeated measure ANOVA for intra-group comparison and for intergroup comparison, independent t-test was applied. There was a significant decline in MMSE score and stroop color word interference score at post-operative period as compared to the baseline values in both the groups up to 4 hours. No such significant difference was seen at 8 hours post-operative period. In both groups, more patients in MF group had mild cognitive dysfunction at 1 hour post-op period, as compared to patient in D group. None of the patients showed severe cognitive impairment. In Group MF, the total number of patients showing signs of delirium was more as compared to group D at Post-op 1 hour. But no signs of delirium were found in any patient in later readings. When presented, the severity of delirium was assessed by Short CAM severity test score. It was observed that all patients who had delirium had CAM severity score of 1 only. The present study concluded that drug dexmedetomidine causes less cognitive decline and less chances of producing post-op delirium as compared to midazolam-fentanyl combination when used for sedation at the time of surgery.

Keywords: Delirium assessment; Dexmedetomidine; Fentanyl, Midazolam; middle ear surgery; MMSE score; psychomotor recovery; sedation; Short CAM; Short CAM severity score.

Sedative agents are routinely used in all surgeries. They help reduce stress, anxiety and minimize their discomfort. An ideal sedation agent should have rapid induction, should be able to provide stable operating conditions with minimal side effects and rapid post-op recovery.[1]Patient-deûned recovery mainly emphasize on physiological and physical function parameters, but actually recovery also includes cognitive and psychomotor domains[2]; which is often ignored in clinical practice.

Postoperative cognitive dysfunction arises after surgery in form of memory impairment and impaired performance on intellectual tasks. It also includes acute delirium. Baseline cognitive performance tests are used for diagnosis of POCD. Comparison of patient's cognitive performance to his own baseline values helps in assessing 'cognitive recovery'. POCD results from numerous contributory factors like age, educational level, and mental health of the patient. Risk of development of POCD increases with advancing age in elderly patients. Minor surgical procedures have low risk of developing POCD. With early recognition and management of potential perioperative risk factors, POCD can be prevented. Delirium is an easily recognizable state whose symptoms may or may not be related to underlying organic disease. Delirium is an independent predictor of many adverse outcomes such as morbidity and mortality.[3]

In the current era, one of the commonly used drugs for sedation in surgeries under local anesthesia are midazolam, dexmedetomidine, and fentanyl. Fentanyl is a ì-selective opioid agonist. It has rapid onset of action with duration of action of nearly 30–60 minutes. Side effects may include respiratory depression, serotonin syndrome, and hypotension.[4]Midazolam, a rapidly acting drug belonging to benzodiazepines class of drug and its effects last for one to six hours. After repeated administration of midazolam, there may be delayed recovery and increased incidence of side effects like excessive sleepiness and psychomotor impairment.[5]Dexmedetomidine is an $á_2$ agonist having sedative, analgesic and sympatholytic properties. When dexmedetomidine is used for sedation, patients remain easily arousable and have minimal effect on respiration.[6]

In this study, we tried to compare these drugs for their effects on post-operative psychomotor functions of the patients.

MATERIALS AND METHODS

This prospective, randomized, controlled, double blind study was conducted after obtaining institutional ethics committee approval. 72 patients of either sex, aged between 18 and 60 years and falling into Grade I/II of American Society of Anesthesiologists (ASA) classification were included in the study. The sample size of 72 was calculated by taking a difference of 8 minutes in post-operative recovery event from the previous study ¯Psychomotor recovery of dexmedetomidine compared with propofol after sedation during spinal anesthesia with the power of 80% and 5% á error.

Written informed consent was obtained from all of them. Pregnant and lactating females, patients with known sensitivity to lignocaine and other study drugs were excluded from the study. Using a computer-based randomization scheme, patients were divided into two groups (36 patients each) i.e. Group D (dexmedetomidine) and Group MF (midazolam fentanyl). Group D patients received dexmedetomidine1µg/kg IV over 10 minutes later followed by continuous infusion starting from 0.3 µg/kg/hr. This was incremented by 0.1µg/kg/hr up to 0.7 µg/kg/hr till an adequate sedation score was achieved (Ramsay sedation scale =3). Group MF patients were given injection midazolam 0.03 mg/kg IV and injection fentanyl 1µg/kg IV bolus over 10 minutes followed by continuous midazolam infusion, 0.03 – 0.07 mg/kg/hr and fentanyl, 0.5 – 1.5 µg/kg/hr till adequate sedation score was achieved. Baseline psychomotor assessment by Mini mental state examination (MMSE)[7]& stroop color word interference test[8], and delirium assessment by short confusion assessment method (CAM)[9] and its severity was assessed by short CAM – severity score[10] at 30 min pre-op & post-operatively at 1, 2, 4 & 8 hours.

MMSE was used to examine psychomotor functions like registration (ability to repeat, retain & recall unrelated words), orientation (to time, place and person), attention, language, recall and ability to follow simple commands. MMSE was scored depending on the number of correctly answered

questions and correctly completed activities. Lower scores indicated poorer performance and greater cognitive impairment. Maximum possible score was 30. On the basis of score obtained from patients, they were further divided into three sub groups. Score between 24-30 was indicative of no cognitive impairment while score between 18-23 indicated mild cognitive impairment and score between 0-17 corresponded to severe cognitive impairment.

In the stroop color word interference test, a sheet on which colour names were printed using four different colors, was given to the patient. No colour name was printed in its matching colour. Eg the word 'blue' will not be printed in blue colour. Patients were given a total of 52 color names to read, either in Hindi and English as per convenience of the patient and then patients were asked to quickly name aloud, the color of the ink in which the word was printed, within 120s time period. Interference score was calculated by no. of items properly named in 120 seconds – no. of errors made.

Presence or absence of delirium in the patient was assessed by short CAM. Short CAM helped in assessing four clinical features of delirium. The first clinical feature to be assessed was acute alteration in mental status with respect to baseline (1a). 2nd feature of focus was inattention i.e. whether the patient was easily distractible or unable to follow has been said/ follow simple commands (2a). It was also assessed whether this inattention behavior fluctuated during the interview (2b). The 3rd feature was based upon disorganized thinking pattern of the patient, like irrelevant conversation or illogical flow of ideas (3a) and whether this disorganized thinking pattern fluctuated during the interview (3b). The 4th feature was based on altered level of consciousness i.e. whether the patient is alert, vigilant, lethargic, having stupor or in coma (4a). It was also assessed whether this behavior fluctuated during the interview (4b). The patients were considered to be in the state of delirium if there was acute change in mental status of the patient (1a=1) or there was fluctuation in abnormal behavior of the patient in terms of inattention or disorganized thinking or consciousness (2b or 3b or 4b = 1) and there was mild or marked difficulty in focusing attention (2a = 2,3 respectively) along with either mild to marked disorganized thinking (3a=2,3 respectively) or altered level of consciousness like vigilant, lethargic, stupor or coma (4a=2,3,4,5 respectively). Number of patients showing signs of delirium was calculated at each time of assessment.

If delirium was found to be present then severity of delirium was assessed by short CAM–severity score. Scores were then assigned to features according to presence & severity of symptoms. Absence of feature was assigned a score of zero (0), mild symptoms were assigned a score of one (1) and a score of two (2) was assigned when features were present in marked form. Total scores of all the features were added up to obtain the severity score of the patient. The score ranged from 0-7. A higher total score indicated more severe delirium. Mean delirium severity score of the patients was calculated by adding the delirium severity scores of all patients and dividing it by total no. of patients.

Statistical Analysis

All the collected data were filled into a master-chart in a Microsoft Excel Sheet. Mean ± S.D. was calculated for quantitative data. For intra group comparison, paired t-test and Repeated measure ANOVA was used. For intergroup comparison, independent t-test was applied. Post-hoc bonferroni test is used if p value <0.05. $p<0.05$ is considered as statistically significant.

RESULTS

This study recruited seventy-two patients who were undergoing elective middle ear surgery under local anesthesia. The drugs were allocated as per their respective group. The Mean ± SD of age in years of patients in their respective group were calculated by using SPSS software version 22. The demographic data of 2 groups of patients was comparable. [Table 1]

The MMSE score and Stroop color word interference test score were calculated at post-op 1,2,4 and 8 hour. On Intra group comparison at different time intervals showed a highly significant decline in MMSE score at 1 hour, 2 hour and 4 hour post operatively as compared to the baseline values in both the groups. At 8 hours post-operative period, no significant difference in MMSE score was seen as compared to baseline. However, on inter group comparison, the difference between the

MMSE score were significant only at 1 & 2 hours post operatively. (Table 2)

5 patients in MF group had mild cognitive dysfunction (MMSE score 18-23) at 1 hour post-op period, as compared to only 1 such patient in D group. None of the patients showed severe cognitive impairment (MMSE score 0-17) in any of the group at any time interval.

The results of the stroop color word interference test score are shown in Table 2. Although both the groups showed a highly significant decline in the stroop color word interference score at 1 hour, 2 hour & 4 hours, as compared to the baseline value, but in intergroup comparison, values were seen to be significantly different only at 2 hours post-op period.

Short CAM test results indicated that more number of patients showed signs of delirium in group MF (27.78%)as compared to group D (11.11%) at Post-op 1 hour. But no signs of delirium were found in any patient at post-op 2 hours, 4 hours and 8 hours in both the groups.

When delirium was present in any patient then the severity of delirium was assessed by Short CAM severity test score. Mean values of short-CAM severity scores are shown in Table 3. When

Table 1. Patient demographic profile

	Group D	Group MF
Age in Years (Mean ± SD)	25.28±7.21	27.61±7.86
No. of females	15 (41.67%)	20 (55.55%)
No. of males	21 (58.33%)	16 (44.44%)

Table 2. MMSE& Stroop color word interference test score of patients

	Mini–Mental State Examination score (Mean ± SD)			Stroop color word interference test score (Mean ± SD)		
	Group D	Group MF	Inter group – p value	Group D	Group MF	Inter group - p value
Pre-op	29.64±0.639	29.64±0.543	0.577	53.06±9.795	52.72±10.132	0.725
1 Hour Post-op	26.22±1.19##	25.19±1.43##	0.016*	35.03±6.300##	30.58±5.469##	0.445
2 Hour Post-op	27.58±0.967##	27.03±1.32##	0.001**	38.53±8.248##	37.00±5.575##	0.011*
4 Hour Post-op	28.42±0.996##	27.94±1.094##	0.737	43.83±8.713##	41.86±7.507##	0.389
8 Hour Post-op	29.94±1.638	29.31±0.786	0.663	52.14±9.550	51.22±9.574	0.725

* -Significant difference between the groups ($p \leq 0.05$)
** - Highly significant difference between the groups ($p \leq 0.001$)
- Highly significant difference as compared to the baseline value ($p \leq 0.001$)

Table 3. Delirium assessment of patients

	No. of patients having delirium [n(%)]		Delirium severity scores of patients (Mean ± SD)		
	Group D	Group MF	Group D	Group MF	P value
Pre-op	00	00	00	00	
1 hr post-op	4 (11.11%)	10 (27.78 %)	0.11±0.319	0.28±0.454#	<0.001**
2 hr post-op	00	00	00	00	
4 hr post-op	00	00	00	00	
8 hr post-op	00	00	00	00	

** - Highly significant difference between the groups ($p \leq 0.001$).
# - Significant difference as compared to the baseline value (0).

we compare post-op 1 hour value with the pre-op value of 0, the difference is significant in group MF; however it is not significant in group D.

It is also evident that short-CAM severity score at post-op 1 hour is highly significantly more in group MF as compared to group D. The mean scores at all other time periods were 0 as no patient has delirium.

DISCUSSION

In this study, it was observed that dexmedetomidine and midazolam-fentanyl combination produced highly significant decline in the cognitive status of the patient as seen by the MMSE and Stroop test scores till 4 hours post-op period. However, the MMSE and stroop test score returned back to baseline in less than 8 hours post-op period. Drop in both the scores were significantly more in MF group fentanyl as compared to D group. Hence, it can be interpreted that dexmedetomidine produced less cognitive dysfunction in the patients as compared to midazolam and fentanyl combination till 2 hours post-op period. However, there was no difference in the time taken for psychomotor recovery in both the groups.

Rajaei M et al. in 2019 also compared dexmedetomidine & midazolam for long term effects on cognition in patients undergoing coronary artery bypass graft surgery. However, they did MMSE test, one day before surgery and repeated it 5 and 30 days after surgery. Results from this study were in favor of dexmedetomidine as this group of patients had fewer signs of cognitive impairment than the midazolam group, at 5 and 30 days after surgery.[11]Kermany MPN et. al in 2016, compared dexmedetomidine and remifentanil for their effects on cognitive state in 100 patients undergoing cataract surgery. MMSE scores post operatively and 120 minutes after drug discontinuation were recorded. The authors concluded that dexmedetomidine is more suitable agent for sedation because it causes lesser impairment of cognitive function and better hemodynamic stability.[12]Perika T et. al compared dexmedetomidine and propofol for psychomotor recovery after sedation during spinal anesthesia. In their study psychomotor recovery was assessed by a battery of tests, postoperatively half hourly for initial 2 hours and later by hourly assessment up to 4 hours. Psychomotor recovery, in patients who received dexmedetomidine was achieved earlier as compared to patients receiving propofol.[13]

In our study delirium was assessed by Short CAM test and lesser number of patients from Group D showed signs of delirium as compared to group MF at post-op 1 hour. But no signs of delirium were found in any patient later on. Similar results were also obtained when Mean Short CAM delirium severity test score at post-op 1 hour as compared to the pre-op value of 0. On intergroup comparison, mean Short-CAM delirium severity score was significantly higher in group MF as compared to group D at 1 hour post-op period. However, all patients where delirium was present, it was mild in severity, as evidenced by severity score of 1 in all of them. Thus, we can interpret that both group of drugs produce only mild delirium. However, chances of producing delirium are lower with dexmedetomidine as compared to Midazolam-fentanyl.

A study conducted by Zhang W et al. in 2020 compared the effects of dexmedetomidine with normal saline on post-operative delirium. The data from 218 patients revealed that there is decreased incidence of post-operative delirium in dexmedetomidine group (18.2%) as compared to normal saline group (30.6%).[14]Thus they concluded that dexmedetomidine might have a protective effect against post-op cognitive dysfunction. Similar findings were noted by Xian Su in 2011 who studied the effect of dexmedetomidine in elderly patients for prevention of delirium during post operative period. Twice daily assessment of delirium with the CAM for intensive care units (CAM-ICU) revealed that prophylactic role of low-dose dexmedetomidine significantly decreased the occurrence of delirium during first 1 week of surgery. during the first 7 days after surgery.[15] Another study done by R R Riker in 2009, compared the effect of dexmedetomidine versus midazolam in critically ill patients and concluded that the prevalence of delirium during treatment was less in dexmedetomidine treated patients (54%) as compared to in midazolam-treated patients (76.6%).[16]A study was done by Azeem TMA et al. in 2018 which compared the effect of dexmedetomidine with morphine and midazolam in patients of cardiac surgery. Prevalence of

delirium was assessed in this study by using CAM-ICU. Assessment was done once daily until 7 days after surgery. This study concluded that incidence of postoperative delirium caused by dexmedetomidine was not significantly different from morphine and midazolam.[17] The results of our study differ from this study possibly due to longer follow-up and selection of patients from ICU.

Thus the effect of dexmedetomidine on delirium is seen to be different in different studies. Thus more studies might be needed to clear this confusion.

CONCLUSION

The present study concluded that drug dexmedetomidine causes less cognitive decline and less chance of producing post-op delirium as compared to midazolam-fentanyl combination when used for sedation at the time of surgery.

Conflict of Interest

There is no conflict of interest.

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